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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/655,547 | 09/04/2003 | Robert Michael Roberts | UVMO:003USC1 | 5542 |

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| EXAMINER | |
|---|---|
| CHEU, CHANGHWA J | |
| **ART UNIT** | **PAPER NUMBER** |
| 1641 | |

DATE MAILED: 01/09/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/655,547 | ROBERTS ET AL. | |
| | Examiner | Art Unit | |
| | Jacob Cheu | 1641 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *01 September 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *182-196* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *182-196* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

Applicant's amendment and affidavit filed on 9/1/2005 has been received and entered into record and considered.

Currently, claims 182-196 are under examination.

### *Claim Rejections - 35 USC § 112*

### *Written Description*

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 182-196 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 182-196 are drawn to a method for detecting pregnancy in a bovine animal. Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula, [or] chemical name' of the claimed

subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court also stated that

> "[A] generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is." (emphasis added)

The court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that "the written description requirement can be met by 'show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. " Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here. A disclosure that does not adequately describe a product itself logically cannot adequately describe a method of using that product (emphasis added).

Thus, the instant specification may provide an adequate written description of the species, such as PAG4, 6, 7, 16, 17, 20, 21, per Lily by structurally describing a representative number of PAGs that are capable of being an early pregnancy detector of bovine and become undetectable about 2 months post-partum, or by describing "structural features common to the members of the genus, which features constitute a substantial portion of the genus." Alternatively, per Enzo, the specification can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

In this case, the specification does not describe all the PAGs required to practice the method of claim 182 in a manner that satisfies either the Lilly or Enzo standards. The specification does not provide the complete structure of any PAG, nor does the specification provide any physical or chemical characteristics of the other PAGs nor any functional characteristics coupled with a known or disclosed correlation between structure and function.

The specification describes only a few PAGs where structural diversities exist among the different PAGs, ranging from 50% to 90% homology (See Figure 4 in both protein and nucleic acid identity comparison). With such diversity in terms of both amino acid and nucleic compositions among the few representatives (boPAG 1 to boPAG 12), one ordinary skill in the art would not conclude that applicant sufficiently describe a "representative number" of such species. In addition, the specification also does not describe "structural features common to the members of the genus, which features constitute a substantial portion of the genus." As indicated by the case law that "[a] definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than

what it is." 43 USPQ2d at 1405. It is noted that applicant describes some conserved sequences around the catalytic aspartic acid residues (Asp 32 and Asp 215) among some BoPAGs, including boPAG 1-12 (See Figure 1). However, there is no further study correlating this conserved region to the asserted function, such as site-directed mutagenesis. Thus, the specification does not provide an adequate written by merely reciting the function limitations of the PAGs, such as detectable in early pregnancy and undetectable at 2-month post-partum.

***Scope of Enablement***

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 182-196 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for PAGs 4,6,7,16,17,20-21, does not reasonably provide enablement for any PAGs. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Regarding polypeptides of the PAGs, the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can

tolerate only relatively conservative substitutions or no substitutions [see Wells (18 September 1990) "Additivity of Mutational Effects in Proteins." Biochemistry **29**(37): 8509-8517; Ngo *et al.* (2 March 1995) "The Protein Folding Problem and Tertiary Structure Prediction, Chapter 14: Computational Complexity Protein Structure Prediction, and the Levinthal Paradox" pp. 492-495]. However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone [Bork (2000) "Powers and Pitfalls in Sequence Analysis: The 70% Hurdle." Genome Research **10**:398-400; Skolnick and Fetrow (2000) "From gene to protein structure and function: novel applications of computational approaches in the genomic era." Trends in Biotech. **18**(1): 34-39, especially p. 36 at Box 2;" Trends in Genetics **14**(6): 248-250; Smith and Zhang (November 1997) "The challenges of genome sequence annotation or 'The devil is in the details'." Nature Biotechnology **15**:1222-1223; Brenner (April 1999) "Errors in genome annotation." Trends in Genetics **15**(4): 132-133;)

> The current invention recites the method of using PAG to detect early pregnancy in bovine. Applicant submitted affidavit provides support for certain PAG species, such as PAGs 4, 6, 16, 17 and 20 can perform the recited method in detecting early pregnancy bovine animal. However, each PAGs possesses different chemical structure, i.e. amino acid sequence. As discussed before in this Office Action, the specification does not provide any physical or chemical characteristics of the other PAGs, nor any functional

characteristics coupled with a known or disclosed correlation between structure and function. One ordinary skill in the art would not be able to predict other PAGs in the functionality relates to the early pregnancy and post-partum, particularly due to the diversity of the chemical structures and compositions as discussed by several researchers in the field (See above discussion). Although it is also noted that applicant describes some conserved sequences around the catalytic aspartic acid residues (Asp 32 and Asp 215) among some boPAGs, including boPAG 1to boPAG12 (See Figure 1). However, there is no further study correlating this conserved region to the asserted function, such as site-directed mutagenesis. Thus, the instant invention is limited to commensurate with the scope of the specific PAGs had shown concrete data in support of the recited method, not any PAGs of bovine animal.

***Response to Applicant's Arguments***

***Written Description***

## A. Applicant argues that the specification describes PAGs supporting the full claim scope.

Applicant argues that specification provides at least 7 APG with amino acid and nucleic sequence which can perform the recited method, thus the specification provides the complete structure of at least seven PAGs. Applicant's argument has been considered but is not persuasive.

As indicated in the Office Action, it is not mainly the number, i.e. how many PAGs, is disclosed in the specification. It rests also in the correlation of structure and functionality. Examiner pointed out that the specification does not provide sufficient analysis or data

establishing or corroborating such correlation, therefore the specification fails to support the full scope of claims.

## *B. The PAGs disclosed are representatives of the entire claim scope.*

Applicant reiterates specification discloses at least 7 amino acid and nucleic acid sequence of PAGs for the asserted method. Applicant argues, if Office does not consider such number sufficient, what number would deemed to be proper. Further, applicant argues that Office Action "vague reference to structural diversities among different PAGs fails to substantiate a rejection on the grounds that the present specification does not disclose a representative number of species under Eli Lilly" (See Remarks, page 3, last paragraph).

Applicant's arguments have been considered but are not persuasive.

As indicated in this Office Action, it is not mainly the number of the species constituting the full scope of the claim, namely genus. It also needs corroborating evidence, i.e. correlation of functionality and structure, sufficiently to one ordinary skill in the art to conclude applicant possess the whole genus. Second, examiner acknowledges the diversity of structures among the PAGs, however examiner points out that the conserved regions among diversity does not amount to justification of possessing the whole genus without further correlation study. Examiner's position is not vague but clear.

## *C. The disclosure is commensurate with the claims.*

Applicant argues in a substantially similar way as to previous points, namely the 7 PAGs is sufficient representative number. Applicant also shows that there is high level of conservation in Figure 4 among boPAGs at both amino acid and nucleic acid level. Such conservation is further illustrated in comparison Figure 1 (conservative region comparison) and Figure 5

(alignment comparison of structure), the comparison indicating PAGs are naturally produced by bovine animals and that the PAGs share both structural and functional characteristics.

Applicant's arguments have been considered but are not persuasive.

The examiner's rebuttal pertinent to the scope of the claim has been discussed before. Examiner would like to further point out that conservation comparison and/or analysis alone is not sufficient to establish the full scope of genus. For instance, boPAG-1, is not within the scope of the recited method because its longer half-life, i.e. undetectable about 3 months, not 2 months. Applicant's conservation comparison also includes boPAG-1 which is excluded from the recited scope, yet boPAG-1 still share structure similarities and conservation with other PAGs. Thus, merely demonstrates conservative regions among PAGs without further functional correlation study is not sufficient for occupying the whole genus of PAGs with respect to the detection of early bovine pregnancy.

***Scope of Enablement***

## A. Applicant argues that the Action fails to establish a prima facie case of non-enablement.

Applicant argues that examiner fails to demonstrate why seven PAGs alone are not sufficient for the full scope of the claims. Applicant cites MPEP "[e]nablement is satisfied as long as at least one method is provided for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claims" and "[a]n assertion that the disclosure is not commensurate with the scope of the claims must be supported by evidence or reasoning substantiating the doubts advanced" and concludes that the rejection is not met by the standard outlined in MPEP (See Remarks, page 7, second paragraph, MEPE §2164.01(b)).

Applicant's arguments have been considered but are not persuasive.

As discussed earlier in this Office Action, examiner points out that the specification does not provide sufficient detailed instruction and example as to establish a "*reasonable correlation* to the entire scope of the claims"(emphasis added). Furthermore, examiner points out the "*reasoning substantiating the doubts advanced*" with respect to the validity of full scope claims and the potential problem of conservation region analysis (emphasis added). Thus, Office has discharged its burden in providing prima faice case of non-enablement.

***B. Applicant argues that the specification provides an enablement disclosure.***

Applicant argues that the specification discloses substantial similarity among PAGs sequences which can be appreciated by one ordinary skill in the art as to how to make and use of the recited invention. In addition, the affidavits filed by Dr. Green (1st and 2nd ) assert that it merely requires routine screening, not undue experimentation. Thus, the 7 examples alone, e.g. PAGs, demonstrate for the full scope of the claims.

Applicant's arguments have been considered but are not persuasive.

Examiner has acknowledged the few working examples of the PAGs species. The question is whether the few examples are sufficient to apply to the whole genus. As indicated by examiner that the similarity of different PAGs are actually not "substantial", ranging from about 55% to 90% (See Figure 4)(emphasis added). Furthermore, there is no corroborating evidence as to the correlation between these "some similar" but not "substantial" PAGs with respect to the recited detection method. Particularly discussed in this Office Action with respect to the unpredictability of the peptide diversity to the correlated functionality, taken together it would be inevitable to impose undue experimentation to one ordinary skill in the art as to how to use the instant invention (See Scope of Rejection).

***Conclusion***

4. No claim is allowed.

5. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jacob Cheu whose telephone number is 571-272-0814. The examiner can normally be reached on 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on 571-272-0823. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jacob Cheu
Examiner
Art Unit 1641

December 10, 2005

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12/12/05